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Cross-coupling of 1-aryl-5-bromopyrazoles: regioselective synthesis of 3,5-disubstituted 1-arylpyrazoles

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Abstract

The cross-coupling of 1-aryl-5-bromopyrazoles **4** with alkynes, vinyltins and arylboronic acids promoted by $Pd(PPh_3)_4$ afforded unsymmetrical 3,5-disubstituted 1-arylpyrazoles **5-8** in excellent yields. 1-Aryl-5-bromopyrazoles **4** were prepared from their corresponding 1-arylpyrazolones **3** with PBr_3 in refluxing acetonitrile.

Condensation of 1,3-diketones and their equivalent 1,3-dienophilic synthons such as propargylic ketones with arylhydrazines has been widely used for synthesis of *N*-arylpyrazoles, often producing two regioisomers in the case of 3,5-disubstituted pyrazoles.[1] Another powerful tool is aromatic substitution of *N*-nonsubstituted pyrazoles with activated halogenated aromatics. This method, however, faces the same regiochemistry issue because pyrazole is an ambident nucleophile.[2] Although there are reports on regio-controlled synthesis of pyrazoles, they have had limited application.[3] Because we required a variety of 3,5-disubstituted 1-arylpyrazole, we needed a general regio-controlled approach to this class of compounds. In this communication, we are pleased to report that cross-coupling of readily available 1-aryl-5-bromopyrazoles[4,5] with terminal alkynes,[6] organostannanes[7] and arylboronic acids[8] gives unsymmetrical 3,5-disubstituted 1-arylpyrazoles in excellent yields.

1-Aryl-5-bromopyrazoles were prepared as shown in Scheme 1. Pyrazolones **3** were made in good to excellent yields from condensation of ketoesters **1** with arylhydrazines **2** in refluxing acetic acid using a known method.[9] Pyrazolones **3** were then converted to 5-bromopyrazoles **4** with PBr_3 in refluxing acetonitrile in 70–85% yields.[10] Usually, less than 15% of the starting pyrazolones **3** was recovered from these reactions, and highly soluble 5-bromopyrazoles **4** were easily taken up into less polar solvents such as a mixture of hexane and ethyl acetate.

The cross coupling of 5-bromopyrazoles **4a–d** with terminal acetylenes was conducted in Et_3N as solvent at 70°C, and was promoted by $Pd(PPh_3)_4/CuBr{\cdot}SMe_2$. Greater than 90% yield of

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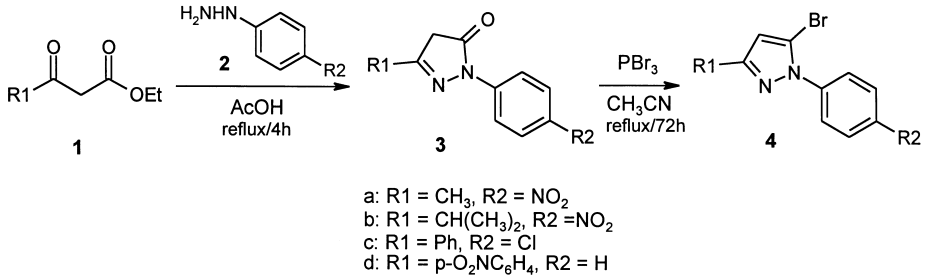


Scheme 1.

products **5**–**8a** were isolated as shown in Table 1. Similarly, the Stille reaction of **4a**–**d** with vinylstannane in THF at reflux for 4–6 h led to 5-vinylpyrazoles **5**–**8b** in excellent yields. Similar result (**5**–**8c**, Table 1) was also obtained from the Suzuki coupling between 5-bromopyrazole **4a**–**d** and arylboronic acids. Actually, the crude coupling products of **4** with acetylenes and arylboronic acids were clean enough for further elaboration with no need of purification. In an effort to prepare a large quantity of **6b**, the coupling of **4b** with propargyl alcohol was achieved with only 0.01 mol% $PdCl_2$ (with two equiv. of PPh_3) using triethylamine as a base in refluxing THF, and **6b** was obtained in quantitative yield. The same low loading of $PdCl_2/2PPh_3$ was also effective for the coupling of **4b** with phenylboronic acid. These results clearly indicate that the cross coupling reaction can serve as a general approach for synthesis of unsymmetrical 3,5-disubstituted 1-aryl-pyrazoles from their corresponding 5-bromopyrazoles.

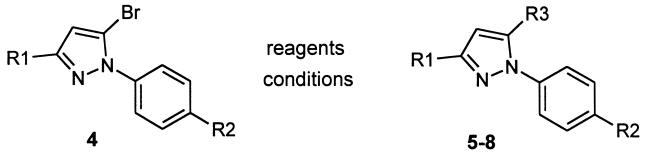
The following are representative procedures:

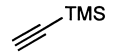
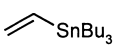
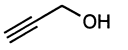
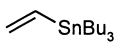
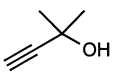
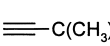
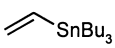
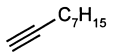
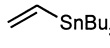
1-(4-Chlorophenyl)-3-phenyl-5-bromopyrazole (**4c**): to a solution of pyrazolone **2c** (2.00 g, 7.38 mmol) in acetonitrile (5 mL) was added PBr_3 (4.0 mL, 37 mmol) and the mixture was heated to reflux for 72 h. After being cooled to 0°C, the mixture was slowly quenched with ice/water and extracted with a 5:1 mixture of hexane and ethyl acetate. The extract was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane:acetate, 15:1) to give **4c** as a white solid (2.10 g, 84%). Mp: 88–89°C. ^{1}H NMR (400 MHz, $CDCl_3$) 7.86 (d, J = 7.0 Hz, 2H), 7.63, 7.52 (ABq, J = 9.0 Hz, 4H) 7.47 (dd, J = 7.0, 7.5 Hz, 2H), 7.38 (m, 1H), 6.84 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) 153.7, 137.9, 134.7, 132.5, 129.6, 129.2, 129.0, 127.3, 126.1, 114.0, 108.5. MS m/e 333 (MH^+). Anal. calcd for $C_{15}H_{10}ClBrN_2$: C, 54.00; H, 3.02; N, 8.40; Cl, 10.63. Found: C, 53.89; H, 2.93; N, 8.38; Cl, 10.77.

The cross-coupling of **4c** with alkyne: to a solution of 5-bromopyrazole **4c** (300 mg, 0.90 mmol) in triethylamine (5 mL) was added $Pd(PPh_3)_4$ (21 mg, 0.018 mmol) and $CuBr{\cdot}SMe_2$ (8 mg, 0.036 mmol), followed by 2-methyl-3-butyn-2-ol (0.10 mL, 0.99 mmol). The mixture was heated to 70°C for 1 h and cooled to room temperature. The solid was filtered off and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (hexane:acetate, 4:1) to give pyrazole **7a** (286 mg, 94%). Mp: 112–113°C. ^{1}H NMR (400 MHz, $CDCl_3$) 7.89 (d, J = 7.0 Hz, 2H), 7.83 (d, J = 8.5 Hz, 2H) 7.48–7.38 (m, 5H), 6.92 (s, 1H), 1.61 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) 152.5, 138.7, 133.5, 132.6, 129.3, 129.2, 128.8, 126.2, 125.8, 124.8, 110.5, 110.4, 102.1, 72.0, 66.0. MS m/e 337 (MH^+). Anal. calcd for $C_{20}H_{17}ClN_2O$: C, 71.32; H, 5.09; N, 8.32; Cl, 10.53. Found: C, 71.25; H, 5.03; N, 8.23; Cl, 10.80.

The cross-coupling of **4a** with vinyl tributyltin: to a solution of 5-bromopyrazole **4a** (138 mg, 0.49 mmol) in THF(5 mL) was added $Pd(PPh_3)_4$ (21 mg, 0.018 mmol) followed by vinyl tributyltin (0.16 mL, 0.54 mmol). The mixture was heated to reflux for 6 h under N_2, it was then quenched

Table 1
Cross couplings of 5-bromopyrazoles **4** with terminal acetylenes, boronic acids and vinyl tins



substrates	reagents	conditions[a]	R1	R2	R3	yields(%)[b,c]
4a[11]		A	CH_3	NO_2		95(**5a**)
4a		B	CH_3	NO_2		92(**5b**)
4a	$PhB(OH)_2$	C	CH_3	NO_2	Ph	94(**5c**)[12]
4b		A	$CH(CH_3)_2$	NO_2		91(**6a**)
4b		B	$CH(CH_3)_2$	NO_2		90(**6b**)
4b	$PhB(OH)_2$	C	$CH(CH_3)_2$	NO_2	Ph	93(**6c**)
4c[13]		A	Ph	Cl		96(**7a**)
4c		B	Ph	C		95(**7b**)
4c	$p\text{-}MeOC_6H_4B(OH)_2$	C	Ph	C	$p\text{-}MeOC_6H_4$	95(**7c**)[3c]
4d		A	$p\text{-}NCC_6H_4$	H		94(**8a**)
4d		B	$p\text{-}NCC_6H_4$	H		90(**8b**)
4d	$p\text{-}MeOC_6H_4B(OH)_2$	C	$p\text{-}NCC_6H_4$	H	$p\text{-}MeOC_6H_4$	97(**8c**)

a) condition A: 2% $Pd(PPh_3)_4$, 4% $CuBr{\cdot}SMe_2$,Et_3N/70°C/1h. B: 2% $Pd(PPh_3)_4$, THF/reflux/4-6h. C: 2% $Pd(PPh_3)_4$, 2M Na_2CO_3/THF/reflux/4h.
b) Isolated yield by column chromatography on silica gel.
c) All products had satisfied ^1H and ^{13}C NMR, MS, high resolution MS or elemental analysis.

with saturated KF and extracted with EtOAc. The extract was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane:acetate, 10:1) to give pyrazole **5b** (103 mg, 92%). ^1H NMR (400 MHz, $CDCl_3$) 8.37, 7.70 (ABq, J = 9.0 Hz, 4H), 6.59 (dd, J = 17.6, 11.0 Hz, 1H), 6.46 (s, 1H), 5.82 (dd, J = 17.6, 1.0 Hz, 1H), 5.47 (dd, J = 11.0, 1.0 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) 151.4, 146.3, 144.9, 142.7, 125.1, 124.8, 124.6, 119.2, 106.8, 13.9. MS m/e 230 (MH^+). Anal. calcd for $C_{17}H_{13}ClN_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.76; H, 4.90; N, 18.15.

The cross-coupling of **4c** with arylboronic acids: to a solution of 5-bromopyrazole **4c** (200 mg, 0.60 mmol) in THF (5 mL) was added $Pd(PPh_3)_4$ (14 mg, 0.012 mmol) and 4-methoxyphenylboronic acid (110 mg, 0.7 mmol), followed by 2 M Na_2CO_3 (1.0 mL, 2.0 mmol). The mixture was heated to reflux for 4 h, and then quenched with water and extracted with EtOAc. The extract was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane:acetate, 15:1) to give pyrazole **7c** (210 mg, 97%). Mp: 104–105°C (lit.[3c] 104–106°C).

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